HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RINVOQ safely and effectively. See full prescribing information for RINVOQ.

RINVOQ® (upadacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2019

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), and THROMBOSIS
See full prescribing information for complete boxed warning.

- **Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with RINVOQ if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase (JAK) inhibitor vs. tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients. (5.2)**
- **Malignancies have occurred in patients treated with RINVOQ. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients. (5.3)**
- **Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred in patients treated with RINVOQ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers. (5.5)**

RECENT MAJOR CHANGES

Indications and Usage (1.7)	10/2022
Indications and Usage (1.5)	5/2023
Dosage and Administration (2.7, 2.9, 2.10, 2.11)	10/2022
Dosage and Administration (2.7, 2.10, 2.11)	5/2023
Warnings and Precautions (5.7, 5.11)	5/2023

INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of:

- Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers. (1.1)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine. (1.1)
- Adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. (1.2)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine. (1.2)
- Adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable. (1.3)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants. (1.3)
- Adults with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers. (1.4)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine. (1.4)
- Adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers. (1.5)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for Crohn's disease, or with potent immunosuppressants such as azathioprine and cyclosporine. (1.5)
- Adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers. (1.6)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine. (1.6)
- Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy. (1.7)
  Limitations of Use
  RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine. (1.7)

DOSAGE AND ADMINISTRATION

- Prior to treatment update immunizations and consider evaluating for active and latent tuberculosis, viral hepatitis, hepatic function, and pregnancy status (2.1)
- Avoid initiation or interrupt RINVOQ if absolute lymphocyte count is less than 500 cells/mm^3, absolute neutrophil count is less than 1000 cells/mm^3, or hemoglobin level is less than 8 g/dL. (2.1, 2.10)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis

- The recommended dosage is 15 mg once daily. (2.3, 2.4, 2.8, 2.9)

Atopic Dermatitis

- *Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less Than 65 Years of Age:* Initiate treatment with 15 mg orally once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg orally once daily. (2.5)
- *Adults 65 Years of Age and Older*: Recommended dosage is 15 mg once daily. (2.5)
- *Severe Renal Impairment*: Recommended dosage is 15 mg once daily. (2.10)

Ulcerative Colitis

- *Adults:* The recommended induction dosage is 45 mg once daily for 8 weeks. The recommended maintenance dosage is 15 mg once daily. A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue RINVOQ if adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response. (2.6)
- See the Full Prescribing Information for the recommended dosage in patients with renal or hepatic impairment and for dosage modification due to drug interactions. (2.10, 2.11)

Crohn's Disease

- *Adults:* The recommended induction dosage is 45 mg once daily for 12 weeks. The recommended maintenance dosage is 15 mg once daily. A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue RINVOQ if an adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response. (2.7)
- See the Full Prescribing Information for the recommended dosage in patients with renal or hepatic impairment and for dosage modification due to drug interactions. (2.10, 2.11)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg, 30 mg, and 45 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to upadacitinib or any of the excipients in RINVOQ. (4, 5.6)

WARNINGS AND PRECAUTIONS

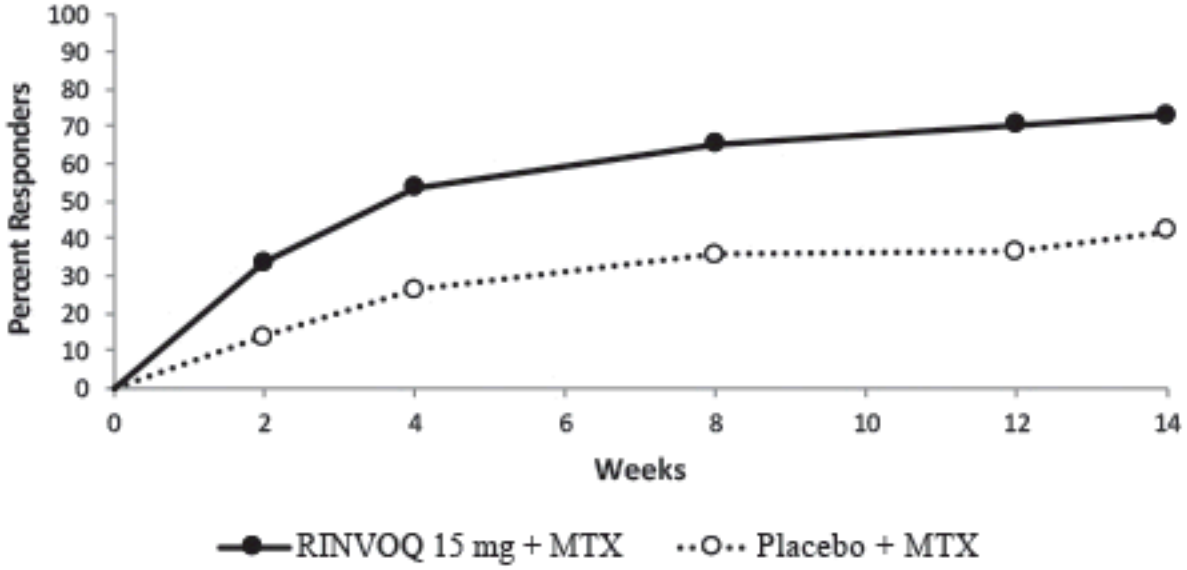
- Serious Infections: Avoid use in patients with active, serious infection, including localized infections. (5.1)
- Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. Discontinue if a serious hypersensitivity reaction occurs. (5.6)
- Gastrointestinal (GI) Perforations: Monitor patients at risk for GI perforations and promptly evaluate patients with symptoms. (5.7)
- Laboratory Abnormalities: Monitoring recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.8)
- Embryo-Fetal Toxicity: May cause fetal harm based on animal studies. Advise female patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.9, 8.1, 8.3)
- Vaccinations: Avoid use with live vaccines. (5.10)

Baseline	21.2 (22.1)	23.0 (27.4)	14.5 (17.3)	14.0 (16.5)	12.6 (14.0)	16.6 (19.2)	18.0 (21.5)	17.9 (22.5)	16.3 (21.1)	16.3 (18.6)
Week 12/14	10.9 (14.9)	4.2 (8.8)	12.8 (21.4)	3.7 (7.8)	13.1 (15.5)	4.6 (9.6)	16.2 (19.8)	5.5 (10.9)	13.9 (17.3)	5.0 (14.0)

Abbreviations: ACR = American College of Rheumatology; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-reactive protein; cDMARDs = conventional disease-modifying anti-rheumatic drugs; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo

[a] Data shown are mean (standard deviation).
[b] Primary efficacy timepoint is at Week 14.
[c] Visual analog scale: 0 = best, 100 = worst.
[d] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Figure 1. Percent of Patients Achieving ACR20 in Trial RA-IV



Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement; MTX = methotrexate
Patients who discontinued randomized treatment, or were missing ACR20 results, or were lost-to-follow-up or withdrawn from the trial were imputed as non-responders.

In RA-I and RA-IV, a higher proportion of patients treated with RINVOQ 15 mg alone or in combination with MTX, achieved DAS28-CRP < 2.6 compared to MTX or placebo at the primary efficacy timepoint (Table 12).

Table 12: Proportion of Patients with DAS28-CRP Less Than 2.6 with Number of Residual Active Joints at Primary Efficacy Timepoint

	Trial RA-I MTX-naïve	
	Monotherapy	
DAS28-CRP Less Than 2.6	**MTX** N = 314	**RINVOQ 15 mg** N = 317
Proportion of responders at Week 12 (n)	14% (43)	36% (113)
Of responders, proportion with 0 active joints (n)	51% (22)	45% (51)
Of responders, proportion with 1 active joint (n)	35% (15)	23% (26)
Of responders, proportion with 2 active joints (n)	9% (4)	17% (19)
Of responders, proportion with 3 or more active joints (n)	5% (2)	15% (17)
	Trial RA-IV MTX-IR	
	Background MTX	
DAS28-CRP Less Than 2.6	**PBO** N = 651	**RINVOQ 15 mg** N = 651
Proportion of responders at Week 12 (n)	6% (40)	29% (187)
Of responders, proportion with 0 active joints (n)	60% (24)	48% (89)
Of responders, proportion with 1 active joint (n)	20% (8)	23% (43)
Of responders, proportion with 2 active joints (n)	15% (6)	13% (25)
Of responders, proportion with 3 or more active joints (n)	5% (2)	16% (30)
Abbreviations: CRP = c-reactive protein; DAS28 = Disease Activity Score 28 joints; MTX = methotrexate; PBO = placebo; IR = inadequate responder		

Radiographic Response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score, at Week 26 in Trial RA-IV and Week 24 in Trial RA-I. The proportion of patients with no radiographic progression (mTSS change from baseline ≤ 0) was also assessed.

In Trial RA-IV, treatment with RINVOQ 15 mg inhibited the progression of structural joint damage compared to placebo in combination with cDMARDs at Week 26 (Table 13). Analyses of erosion and joint space narrowing scores were consistent with overall results.

In the placebo plus MTX group, 76% of the patients experienced no radiographic progression at Week 26 compared to 83% of the patients treated with RINVOQ 15 mg.

In Trial RA-I, treatment with RINVOQ 15 mg monotherapy inhibited the progression of structural joint damage compared to MTX monotherapy at Week 24 (Table 13). Analyses of erosion and joint space narrowing scores were consistent with overall results.

In the MTX monotherapy group, 78% of the patients experienced no radiographic progression at Week 24 compared to 87% of the patients treated with RINVOQ 15 mg monotherapy.

Table 13: Radiographic Changes

	Trial RA-IV MTX-IR

	Background MTX		
mTSS	PBO (N=651) Mean (SD)	RINVOQ 15 mg (N=651) Mean (SD)	Estimated Difference vs PBO at Week 26 (95% CI)[a]
Baseline	35.9 (52)	34.0 (50)	
Week 26[b]	0.78 (0.1)	0.15 (0.1)	-0.63 (-0.92, -0.34)
	Trial RA-I MTX-naïve		
	Monotherapy		
	MTX (N=309) Mean (SD)	RINVOQ 15 mg (N=309) Mean (SD)	Estimated Difference vs MTX at Week 24 (95% CI)[c]
Baseline	13.3 (31)	18.1 (38)	
Week 24[d]	0.67 (2.8)	0.14 (1.4)	-0.53 (-0.85, -0.20)

Abbreviations: mTSS = modified Total Sharp Score, MTX = methotrexate; PBO = placebo; SD = standard deviation; IR = inadequate responders; bDMARDs = biologic disease modifying anti-rheumatic drugs; LS = least squares; CI = confidence intervals

[a] LS means and 95% CI based on a random coefficient model fit to the mTSS value adjusting for time, treatment group, prior bDMARDs use, treatment group-by-time interaction, with random slopes and random intercept.

[b] Estimated linear rate of structural progression by Week 26 and standard errors are presented.

[c] LS means and 95% CI based on a linear regression model fit to change from baseline in mTSS adjusting for treatment group, baseline mTSS, and geographic region.

[d] Mean change from baseline and standard deviation are presented.

Physical Function Response

Treatment with RINVOQ 15 mg, alone or in combination with cDMARDs, resulted in a greater improvement in physical function at Week 12/14 compared to all comparators as measured by HAQ-DI.

Other Health-Related Outcomes

In all trials except for Trial RA-V, patients receiving RINVOQ 15 mg had greater improvement from baseline in physical component summary (PCS) score, mental component summary (MCS) scores, and in all 8 domains of the Short Form Health Survey (SF-36) compared to placebo in combination with cDMARDs or MTX monotherapy at Week 12/14.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in Trials RA-I, RA-III, and RA-IV. Improvement in fatigue at Week 12 was observed in patients treated with RINVOQ 15 mg compared to patients on placebo in combination with cDMARDs or MTX monotherapy.

14.2 Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in two Phase 3 randomized, double-blind, multicenter, placebo-controlled trials in patients 18 years of age or older with

moderately to severely active psoriatic arthritis. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. Although another dose has been studied, the recommended dose of RINVOQ is 15 mg once daily for psoriatic arthritis.

Trial PsA-I (NCT03104400) was a 24-week trial in 1705 patients with moderately to severely active psoriatic arthritis who had an inadequate response or intolerance to at least one non-biologic DMARD. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily, adalimumab, or placebo, alone or in combination with background non-biologic DMARDs. At Week 24, all patients randomized to placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Trial PsA-II (NCT03104374) was a 24-week trial in 642 patients with moderately to severely active psoriatic arthritis who had an inadequate response or intolerance to at least one biologic DMARD. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo, alone or in combination with background non-biologic DMARDs. At Week 24, all patients randomized to placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Clinical Response

In both trials, patients treated with RINVOQ 15 mg achieved significantly higher ACR20 responses compared to placebo at Week 12 (Table 14, Figure 2). A higher proportion of patients treated with RINVOQ 15 mg achieved ACR50 and ACR70 responses at Week 12 compared to placebo.

Treatment with RINVOQ 15 mg resulted in improvements in the ACR components compared to placebo at the primary efficacy timepoint (Table 15).

Table 14: Clinical Response

Trial	**Trial PsA-I non-biologic DMARD-IR**		**Trial PsA-II bDMARD-IR**	
Treatment Group	PBO %	RINVOQ 15 mg % Δ (95% CI)	PBO %	RINVOQ 15 mg % Δ (95% CI)
N	423	429	212	211
ACR20				
Week 12	36	71 35 (28, 41)	24	57 33 (24, 42)
ACR50				
Week 12	13	38 24 (19, 30)	5	32 27 (20, 34)
ACR70				
Week 12	2	16 13 (10, 17)	1	9 8 (4, 12)

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement, bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; PBO = placebo
Patients who discontinued randomized treatment or were missing data at week of evaluation were imputed as non-responders in the analyses.

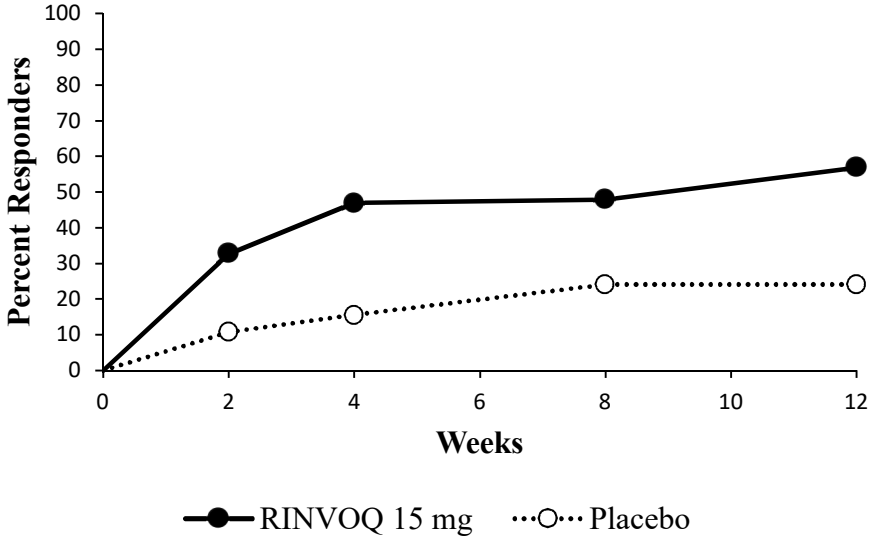
Table 15: Components of ACR Response[a]

Trial	**Trial PsA-I non-biologic DMARD-IR**		**Trial PsA-II bDMARD-IR**	
Treatment Group	PBO (N=423)	RINVOQ 15 mg (N=429)	PBO (N=212)	RINVOQ 15 mg (N=211)
Number of tender/painful joints (0-68)				
Baseline	20.0 (14.3)	20.4 (14.7)	25.3 (17.6)	24.9 (17.3)
Week 12	12.5 (13.3)	8.8 (12.5)	19.3 (18.5)	12.6 (15.6)
Number of swollen joints (0-66)				
Baseline	11.0 (8.2)	11.6 (9.3)	12.0 (8.9)	11.3 (8.2)
Week 12	5.6 (7.2)	3.5 (6.0)	7.3 (9.4)	4.4 (5.7)
Patient assessment of pain[b]				
Baseline	6.1 (2.1)	6.2 (2.1)	6.6 (2.1)	6.4 (2.1)
Week 12	5.1 (2.3)	3.8 (2.4)	5.9 (2.3)	4.4 (2.5)
Patient global assessment[b]				
Baseline	6.3 (2.0)	6.6 (2.0)	6.8 (2.0)	6.8 (1.9)
Week 12	5.2 (2.2)	3.8 (2.3)	6.1 (2.3)	4.5 (2.5)
Disability index (HAQ-DI)[c]				
Baseline	1.1 (0.6)	1.2 (0.7)	1.2 (0.7)	1.1 (0.6)
Week 12	1.0 (0.7)	0.7 (0.6)	1.1 (0.6)	0.8 (0.7)
Physician global assessment[b]				
Baseline	6.5 (1.6)	6.7 (1.6)	6.5 (1.8)	6.5 (1.8)
Week 12	4.3 (2.2)	3.1 (2.0)	5.0 (2.2)	3.4 (2.1)
hsCRP (mg/L)				
Baseline	11.5 (15.8)	11.0 (14.9)	10.4 (18.5)	11.2 (18.6)
Week 12	10.1 (15.2)	4.2 (9.9)	9.4 (13.4)	4.3 (7.9)

Abbreviations: ACR = American College of Rheumatology; hsCRP = high sensitivity c-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; PBO = placebo
[a] Data shown are mean (standard deviation).
[b] Numeric rating scale (NRS): 0 = best, 10 = worst
[c] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percentage of patients achieving ACR20 response by visit is shown in Figure 2.

Figure 2. Percent of Patients Achieving ACR20 in Trial PsA-II



Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement
Patients who discontinued randomized treatment, or were missing ACR20 results, or were lost-to-follow-up or withdrawn from the trial were imputed as non-responders.

Treatment with RINVOQ 15 mg resulted in improvement in dactylitis and enthesitis in patients with pre-existing dactylitis or enthesitis.

Treatment with RINVOQ 15 mg resulted in improvement in skin manifestations in patients with PsA. However, RINVOQ has not been studied in and is not indicated for the treatment of plaque psoriasis.

Physical Function Response

In both trials, patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by HAQ-DI at Week 12 (Table 14). The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 12 was -0.28 (-0.35, -0.22) in Trial PsA-I and -0.21 (-0.30, -0.12) in Trial PsA-II.

The proportion of HAQ-DI responders (≥ 0.35 improvement from baseline in HAQ-DI score) at Week 12 in Trial PsA-I and Trial PsA-II was 58% and 45%, respectively, in patients receiving RINVOQ 15 mg and 33% and 27%, respectively, in patients receiving placebo.

Radiographic Response

In Trial PsA-I, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Total Sharp Score (mTSS) and its components, the erosion score and the joint space narrowing score, at Week 24.

Treatment with RINVOQ 15 mg inhibited progression of structural joint damage compared to placebo at Week 24 (Table 16). Analyses of erosion and joint space narrowing scores were consistent with overall results. The proportion of patients with no radiographic progression

(mTSS change ≤ 0) at Week 24 was 93% in patients receiving RINVOQ 15 mg and 89% in patients receiving placebo.

Table 16: Radiographic Changes in Trial PsA-I

	PBO (N=392) Mean (SD)	**RINVOQ 15 mg** (N=407) Mean (SD)	Estimated Difference vs PBO at Week 24 (95% CI)[a]
mTSS			
Baseline	13.32 (31.2)	13.14 (42.4)	
Week 24[b]	0.23 (0.07)	-0.02 (0.04)	-0.25 (-0.41, -0.09)

Abbreviations: CI = confidence intervals; LS = least squares; mTSS = modified Total Sharp Score; PBO = placebo; SD = standard deviation

[a] LS means and 95% CI based on a random coefficient model fit to the mTSS value adjusting for time, treatment group, current DMARD use (yes/no), treatment group-by-time interaction, with random slopes and random intercept.

[b] Estimated linear rate of structural progression by Week 24 and standard errors are presented.

Other Health-Related Outcomes

Health-related quality of life was assessed by SF-36. In both trials, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared to placebo at Week 12. Greater improvement was also observed in the Mental Component Summary score and all 8 domains of SF-36 compared to placebo.

Patients receiving RINVOQ 15 mg showed greater improvement from baseline in fatigue, as measured by FACIT-F score, at Week 12 compared to placebo in both trials.

14.3 Atopic Dermatitis

The efficacy of RINVOQ 15 mg and 30 mg once daily, was assessed in three Phase 3 randomized, double-blind, multicenter trials (AD-1, AD-2, AD-3; NCT03569293, NCT03607422, and NCT03568318, respectively) in a total of 2584 patients (12 years of age and older). RINVOQ was evaluated in 344 pediatric patients and 2240 adult patients with moderate to severe atopic dermatitis (AD) not adequately controlled by topical medication(s).

Disease severity at baseline was defined by a validated Investigator's Global Assessment (vIGA-AD) score ≥3 in the overall assessment of AD on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16, a minimum body surface area (BSA) involvement of ≥10%, and weekly average Worst Pruritus Numerical Rating Scale (NRS) score ≥4. Overall, 57% of the patients were male and 69% were white. The mean age at baseline was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. At baseline, 49% of patients had a vIGA-AD score of 3 (moderate AD), and 51% of patients had a vIGA-AD score of 4 (severe AD). The baseline mean EASI score was 29 and the baseline weekly average Worst Pruritus NRS score was 7. Approximately 52% of the patients had prior exposure to systemic AD treatment.

In all three trials, patients received RINVOQ once daily oral doses of 15 mg, 30 mg, or matching placebo for 16 weeks. In Trial AD-3, patients also received RINVOQ or placebo with concomitant topical corticosteroids (TCS) for 16 weeks.

All three trials assessed the co-primary endpoints of the proportion of patients with a vIGA-AD score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI score from baseline) at Week 16. Secondary endpoints included EASI-90 and EASI-100 at Week 16, and the proportion of patients with reduction in itch (≥4-point improvement from baseline in the Worst Pruritus NRS) at Weeks 1, 4, and 16. In Trials AD-1 and AD-2, the proportion of patients with reduction in pain (≥4-point improvement in the Atopic Dermatitis Symptom Scale [ADerm-SS] Skin Pain NRS) from baseline to Week 16 was a secondary endpoint.

Clinical Response

Monotherapy Trials (AD-1 and AD-2)

The results of RINVOQ monotherapy trials (AD-1 and AD-2) are presented in Table 17. Figure 3 presents the proportion of patients with ≥ 4-point improvement in Worst Pruritus NRS at Weeks 1, 4, and 16 for Trials AD-1 and AD-2.

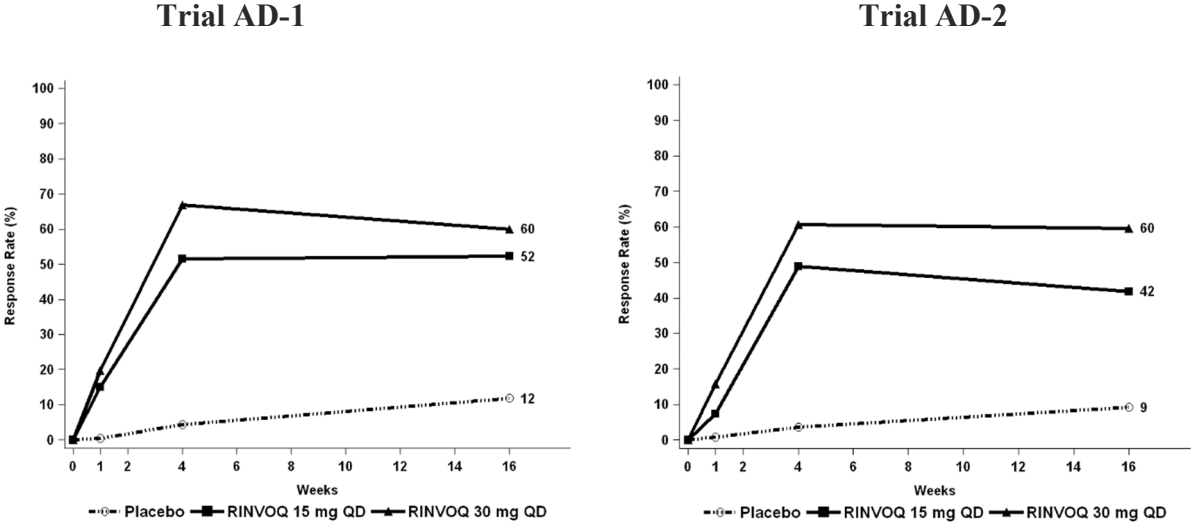
Table 17: Efficacy Results of Monotherapy Trials at Week 16 in Patients with Moderate to Severe AD

	Trial AD-1			Trial AD-2		
	PBO	**RINVOQ 15 mg**	**RINVOQ 30 mg**	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**
Number of patients randomized	281	281	285	278	276	282
vIGA-AD 0/1[a,b]	8%	48%	62%	5%	39%	52%
Difference from PBO (95% CI)		40% (33%, 46%)	54% (47%, 60%)		34% (28%, 40%)	47% (41%, 54%)
EASI-75[a]	16%	70%	80%	13%	60%	73%
Difference from PBO (95% CI)		53% (46%, 60%)	63% (57%, 70%)		47% (40%, 54%)	60% (53%, 66%)
EASI-90[a]	8%	53%	66%	5%	42%	58%
Difference from PBO (95% CI)		45% (39%, 52%)	58% (51%, 64%)		37% (31%, 43%)	53% (47%, 59%)
EASI-100[a]	2%	17%	27%	1%	14%	19%
Difference from PBO (95% CI)		15% (10%, 20%)	25% (20%, 31%)		13% (9%, 18%)	18% (13%, 23%)
Number of patients with baseline Worst Pruritus NRS score ≥ 4	272	274	280	274	270	280
≥ 4-point improvement in Worst Pruritus NRS[c]	12%	52%	60%	9%	42%	60%

Difference from PBO (95% CI)		40% (33%, 48%)	48% (41%, 55%)		33% (26%, 39%)	50% (44%, 57%)
Number of patients with baseline ADerm-SS Skin Pain NRS score ≥ 4	233	237	249	247	237	238
≥ 4-point improvement in ADerm-SS Skin Pain NRS[d]	15%	54%	63%	13%	49%	65%
Difference from PBO (95% CI)		39% (31%, 47%)	49% (41%, 56%)		36% (28%, 43%)	52% (44%, 59%)

Abbreviations: ADerm-SS = Atopic Dermatitis Symptom Scale; PBO = placebo
[a] Based on number of patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of patients whose baseline Worst Pruritus NRS is ≥ 4
[d] Based on number of patients whose baseline ADerm-SS Skin Pain NRS is ≥ 4

Figure 3: Proportion of Patients with Moderate to Severe AD with ≥4-point Improvement in the Worst Pruritus NRS in Monotherapy Trials



Examination of age, gender, race, weight, and prior systemic treatment with immunosuppressants did not identify differences in response to RINVOQ among these subgroups in Trials AD-1 and AD-2.

Concomitant TCS Trial (AD-3)

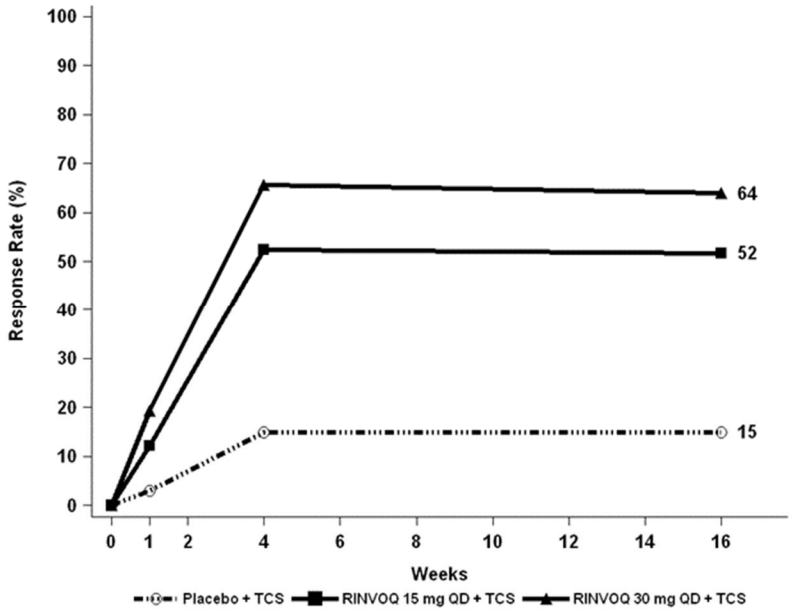
The results of the RINVOQ with concomitant TCS trial (AD-3) are presented in Table 18. Figure 4 presents the proportion of patients with ≥ 4-point improvement in Worst Pruritus NRS at Weeks 1, 4, and 16 for Trial AD-3.

Table 18: Efficacy Results with Concomitant TCS at Week 16 in Patients with Moderate to Severe AD

	Trial AD-3		
	PBO + TCS	**RINVOQ 15 mg + TCS**	**RINVOQ 30 mg + TCS**
Number of patients randomized	304	300	297
vIGA-AD 0/1[a,b]	11%	40%	59%
Difference from PBO (95% CI)		29% (22%, 35%)	48% (41%, 54%)
EASI-75[a,]	26%	65%	77%
Difference from PBO (95% CI)		38% (31%, 45%)	51% (44%, 57%)
EASI-90[a]	13%	43%	63%
Difference from PBO (95% CI)		30% (23%, 36%)	50% (43%, 56%)
EASI-100[a]	1%	12%	23%
Difference from PBO (95% CI)		11% (7%, 14%)	21% (16%, 26%)
Number of patients with baseline Worst Pruritus NRS score ≥ 4	294	288	291
≥ 4-point improvement in Worst Pruritus NRS[c]	15%	52%	64%
Difference from PBO (95% CI)		37% (30%, 44%)	49% (42%, 56%)

Abbreviations: PBO = placebo
[a] Based on number of patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of patients whose baseline Worst Pruritus NRS is ≥ 4

Figure 4: Proportion of Patients with Moderate to Severe AD with ≥4-point Improvement in the Worst Pruritus NRS in Concomitant TCS Trial



Examination of age, gender, race, weight, and prior systemic treatment with immunosuppressants did not identify differences in response to RINVOQ among these subgroups in Trial AD-3.

Pediatric Patient Population

The efficacy results of the RINVOQ monotherapy trials (AD-1 and AD-2) and the RINVOQ with concomitant TCS trial (AD-3) at Week 16 for pediatric patients 12 years of age and older are presented in Table 19 and Table 20, respectively.

Table 19: Efficacy Results of Monotherapy Trials for Pediatric Patients 12 Years of Age and Older with Moderate to Severe AD at Week 16

	Trial AD-1			Trial AD-2		
	PBO	RINVOQ 15 mg	RINVOQ 30 mg	PBO	RINVOQ 15 mg	RINVOQ 30 mg
Number of pediatric patients randomized	40	42	42	36	33	35
vIGA-AD 0/1[a,b]	8%	38%	69%	3%	42%	62%
Difference from PBO (95% CI)		31% (14%, 47%)	62% (45%, 78%)		40% (22%, 57%)	60% (42%, 77%)
EASI-75[a]	8%	71%	83%	14%	67%	74%
Difference from PBO (95% CI)		63% (47%, 79%)	75% (61%, 89%)		53% (33%, 72%)	61% (42%, 79%)
Number of pediatric patients with baseline Worst Pruritus NRS score ≥ 4	39	40	42	36	30	34
≥ 4-point improvement in Worst Pruritus NRS[c]	15%	45%	55%	3%	33%	50%

Difference from PBO (95% CI)	30% (10%, 49%)	39% (21%, 58%)	31% (13%, 48%)	47% (30%, 65%)

Abbreviations: PBO = placebo
[a] Based on number of pediatric patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of pediatric patients whose baseline Worst Pruritus NRS is ≥ 4

Table 20: Efficacy Results with Concomitant TCS for Pediatric Patients 12 Years of Age and Older with Moderate to Severe AD at Week 16

	Trial AD-3		
	PBO + TCS	**RINVOQ 15 mg + TCS**	**RINVOQ 30 mg + TCS**
Number of pediatric patients randomized	40	39	37
vIGA-AD 0/1[a,b]	8%	31%	65%
Difference from PBO (95% CI)		23% (7%, 40%)	57% (40%, 75%)
EASI-75[a]	30%	56%	76%
Difference from PBO (95% CI)		26% (5%, 47%)	46% (26%, 65%)
Number of pediatric patients with baseline Worst Pruritus NRS score ≥ 4	38	36	33
≥ 4-point improvement in Worst Pruritus NRS[c]	13%	42%	55%
Difference from PBO (95% CI)		29% (9%, 48%)	41% (21%, 61%)

Abbreviations: PBO = placebo
[a] Based on number of pediatric patients randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] Based on number of pediatric patients whose baseline Worst Pruritus NRS is ≥ 4

14.4 Ulcerative Colitis

Induction Trials (Study UC-1 and Study UC-2)

In two identical induction trials (UC-1; NCT02819635 and UC-2; NCT03653026), patients were randomized 2:1 to receive either RINVOQ 45 mg once daily or placebo for 8 weeks. A total of 988 patients were analyzed across the two trials. These trials included adult patients with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapy. Enrolled patients were permitted to use stable doses of oral aminosalicylates, methotrexate, ulcerative colitis-related antibiotics, and/or oral corticosteroids (up to 30 mg/day prednisone or equivalent). At baseline, 38% of patients were receiving corticosteroids, and 68% of patients were receiving aminosalicylates. Concomitant biologic therapies, azathioprine, 6-mercaptopurine, intravenous or rectal corticosteroids were prohibited. A total of 51% of patients

had previously failed treatment with or were intolerant to at least one biologic therapy. RINVOQ is indicated for patients who have an inadequate response or intolerance to one or more TNF blockers *[see Indications and Usage (1.4)]*.

Disease activity was assessed on the modified Mayo score (mMS), a 3-component Mayo score (0-9) which consists of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally read endoscopy score (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration. Enrolled patients had a mMS between 5 to 9 with an ES of 2 or 3; at baseline the median mMS was 7, with 61% of patients having a baseline mMS of 5 to 7 and 39% having a mMS of 8 to 9.

At baseline, 39% and 37% of patients received corticosteroids, 1% and 1% of patients received methotrexate, and 68% and 69% of patients received aminosalicylates in UC-1 and UC-2, respectively. Patient disease activity was moderate (mMS ≤7) in 61% and 60% of patients and severe (mMS >7) in 39% and 40% of patients in UC-1 and UC-2, respectively.

The primary endpoint was clinical remission defined using the mMS at Week 8. Secondary endpoints included clinical response, endoscopic improvement, and histologic endoscopic mucosal improvement (see Table 21 and Table 22).

Table 21: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 - Study UC-1

Study UC-1			
Endpoint	**Placebo**	**RINVOQ 45 mg Once Daily**	**Treatment Difference vs Placebo (95% CI)**
Clinical Remission[a]			
Total Population	N=154 5%	N=319 26%	22%[b] (16, 27)
Prior biologic failure[c]	N=78 < 1%	N=168 18%	
Without prior biologic failure	N=76 9%	N=151 35%	
Clinical Response[d]			
Total Population	N=154 27%	N=319 73%	46%[b] (38, 54)
Prior biologic failure[c]	N=78 13%	N=168 64%	
Without prior biologic failure	N=76 42%	N=151 82%	
Endoscopic Improvement[e]			
Total Population	N=154 7%	N=319 36%	29%[b] (23, 36)
Prior biologic failure[c]	N=78 2%	N=168 27%	
Without prior biologic failure	N=76 13%	N=151 47%	
Histologic Endoscopic Mucosal Improvement[f]			
Total Population	N=154 7%	N=319 30%	24%[b] (17, 30)
Prior biologic failure[c]	N=78 1%	N=168 23%	
Without prior biologic failure	N=76 12%	N=151 38%	

[a] Per mMS: SFS ≤1 and not greater than baseline, RBS = 0, ES of ≤ 1 without friability
[b] p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
[c] Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologic treatments for ulcerative colitis.
[d] Per mMS: decrease ≥ 2 points and ≥ 30% from baseline and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤1
[e] ES ≤ 1 without friability
[f] ES ≤1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue)

Table 22: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 - Study UC-2

Study UC-2			
Endpoint	**Placebo**	**RINVOQ 45 mg Once Daily**	**Treatment Difference vs Placebo (95% CI)**
Clinical Remission[a]			
Total Population	N=174 4%	N=341 33%	29%[b] (23, 35)
Prior biologic failure[c]	N=89 2%	N=173 30%	
Without prior biologic failure	N=85 6%	N=168 38%	
Clinical Response[d]			
Total Population	N=174 25%	N=341 74%	49%[b] (42, 57)
Prior biologic failure[c]	N=89 19%	N=173 69%	
Without prior biologic failure	N=85 32%	N=168 80%	
Endoscopic Improvement[e]			
Total Population	N=174 8%	N=341 44%	35%[b] (29, 42)
Prior biologic failure[c]	N=89 5%	N=173 37%	
Without prior biologic failure	N=85 12%	N=168 51%	
Histologic Endoscopic Mucosal Improvement[f]			
Total Population	N=174 6%	N=341 37%	30%[b] (24, 36)
Prior biologic failure[c]	N=89 5%	N=173 31%	
Without prior biologic failure	N=85 7%	N=168 43%	

[a] Per mMS: SFS ≤ 1 and not greater than baseline, RBS = 0, ES of ≤ 1 without friability
[b] p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
[c] Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologic treatments for ulcerative colitis.
[d] Per mMS: decrease ≥ 2 points and ≥ 30% from baseline and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤1
[e] ES ≤ 1 without friability
[f] ES ≤1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue)

Studies UC-1 and UC-2 were not designed to evaluate the relationship of histologic endoscopic mucosal improvement at Week 8 to disease progression and long-term outcomes.

Rectal Bleeding and Stool Frequency Subscores

Onset of clinical response was assessed using the SFS and RBS (partial modified Mayo Score [pmMS]). Initial response was defined as a decrease of ≥1 point and ≥30% from baseline in pmMS and a decrease in RBS ≥1 or an absolute RBS≤1. Onset of response occurred as early as Week 2 in a greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo.

Endoscopic and Histologic Assessment

Normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. At Week 8, a greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo achieved endoscopic remission (UC-1: 14% vs 1%, UC-2: 18% vs 2%). Endoscopic remission with Geboes histologic score < 2.0 (indicating no neutrophils in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was achieved by a greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo at Week 8 (UC-1: 11% vs 1%, UC-2: 13% vs 2%).

Abdominal Pain and Bowel Urgency

A greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo had no abdominal pain (UC-1: 47% vs 23%, UC-2: 54% vs 24%) and no bowel urgency (UC-1: 48% vs 21%, UC-2: 54% vs 26%) at Week 8.

Maintenance Study UC-3

In UC-3 (NCT02819635), a total of 451 patients who received RINVOQ 45 mg once daily in either UC-1, UC-2 or UC-4 and achieved clinical response were re-randomized to receive RINVOQ 15 mg, 30 mg or placebo once daily for up to 52 weeks.

The primary endpoint was clinical remission defined using mMS at Week 52. Secondary endpoints included corticosteroid-free clinical remission, endoscopic improvement, and histologic endoscopic mucosal improvement (see Table 23).

Table 23. Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 52 in Maintenance Study UC-3

Endpoint	Placebo	RINVOQ 15 mg Once Daily	Treatment Difference 15 mg vs Placebo (95% CI)	RINVOQ 30 mg Once Daily	Treatment Difference 30 mg vs Placebo (95% CI)
Clinical remission[a]					
Total Population	N=149 12%	N=148 42%	31%[b] (22, 40)	N=154 52%	39%[b] (30, 48)
Prior biologic failure[c]	N=81 7%	N=71 41%		N=73 49%	
Without prior biologic failure	N=68 18%	N=77 44%		N=81 54%	
Corticosteroid-free clinical remission[d]					
Total Population	N=54 22%	N=47 57%	35%[b] (18, 53)	N=58 68%	45%[b] (29, 62)
Prior biologic failure[c]	N=22 14%	N=17 71%		N=20 73%	
Without prior biologic failure	N=32 28%	N=30 49%		N=38 65%	
Endoscopic Improvement[e]					
Total Population	N=149 14%	N=148 49%	34%[b] (25, 44)	N=154 62%	46%[b] (37, 56)
Prior biologic failure[c]	N=81 8%	N=71 43%		N=73 56%	
Without prior biologic failure	N=68 22%	N=77 54%		N=81 67%	
Histologic Endoscopic Mucosal Improvement[f]					
Total Population	N=149 12%	N=148 35%	24%[b] (15, 33)	N=154 50%	37%[b] (28, 47)
Prior biologic failure[c]	N=81 5%	N=71 33%		N=73 48%	
Without prior biologic failure	N=68 20%	N=77 37%		N=81 52%	

[a] Per mMS: SFS ≤1 and not greater than baseline, RBS = 0, ES ≤1 without friability
[b] p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
[c] Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologic treatments for ulcerative colitis.
[d] Clinical remission per mMS at Week 52 and corticosteroid free for ≥90 days immediately preceding Week 52 among patients who achieved clinical remission at the end of the induction treatment
[e] ES ≤ 1 without friability
[f] ES ≤1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue)

The relationship between histologic endoscopic mucosal improvement at Week 52 and disease progression and longer-term outcomes after Week 52 was not evaluated in Study UC-3.

Endoscopic and Histologic Assessment

Normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. In UC-3, a greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo achieved endoscopic remission at Week 52 (24% and 26% vs 6%). Endoscopic remission with Geboes histologic score < 2.0 was achieved by a greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo at Week 52 (18% and 19% vs 5%).

Abdominal Pain and Bowel Urgency

At Week 52, a greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo had no abdominal pain (46%, 55% and 21%, respectively) and no bowel urgency (56%, 64% and 17%, respectively).

14.5 Crohn's Disease

Induction Trials (Studies CD-1 and CD-2)

In two induction trials, CD-1 (NCT03345836) and CD-2 (NCT03345849), patients were randomized 2:1 to receive RINVOQ 45 mg or placebo once daily for 12 weeks. Efficacy was assessed in a population of 857 patients (419 patients in CD-1 and 438 patients in CD-2) with moderately to severely active Crohn's disease (CD), with baseline Crohn's Disease Activity Index (CDAI) score of at least 220 and centrally-reviewed Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥ 6, or ≥ 4 for isolated ileal disease, excluding the narrowing component. In CD-1, all patients had inadequate response or were intolerant to treatment with one or more biological therapies (prior biologic failure). In CD-2, 45% (197/438) of patients had inadequate response or were intolerant to treatment with one or more biological therapies (prior biologic failure). Enrolled patients in both studies were permitted to use stable doses of CD-related antibiotics, aminosalicylates, or methotrexate. Concomitant corticosteroids (up to 30 mg/day prednisone or equivalent) were permitted at enrollment; tapering was initiated at Week 4.

In CD-1, patients had a mean age of 37 years (range 18 to 74 years); 46% were female; and 72% identified as White, 21% as Asian, 6% as Black or African American, 0.5% as American Indian or Alaska Native, and 0.5% as multiple racial groups. In CD-2, patients had a mean age of 40 years (range of 18 to 74 years); 45% were female; 74% identified as White, 20% as Asian, 4% as Black or African American, and 2% as multiple racial groups.

At baseline, 36% and 37% of patients received corticosteroids, 7% and 3% of patients received methotrexate, 15% and 24% of patients received aminosalicylates, and 2% and 1% of patients received CD-related antibiotics in CD-1 and CD-2, respectively.

The co-primary endpoints were the proportion of patients achieving clinical remission (by CDAI) at Week 12, and the proportion of patients achieving endoscopic response (by SES-CD) at Week 12. Secondary efficacy endpoints included clinical response, corticosteroid-free remission, and endoscopic remission (see Table 24 and Table 25).

Table 24: Proportion of Patients Meeting Primary and Additional Efficacy Endpoints in Induction Study CD-1

CD-1			
Endpoint	**Placebo**	**RINVOQ 45 mg Once Daily**	**Treatment Difference vs Placebo (95% CI)**
Co-Primary Endpoints at Week 12			
Clinical remission[a]	N=146 18%	N=273 36%	17% (9, 25)*
Endoscopic response[b]	N=146 3%	N=273 34%	30% (24, 36)*
Additional Endpoints at Week 12			
Clinical response (CR-100)[c]	N=146 31%	N=273 54%	22% (13, 31)*
Corticosteroid-free clinical remission in patients on corticosteroids at baseline[a,d]	N=53 11%	N=96 30%	17% (5, 29)**
Endoscopic remission[e]	N=146 3%	N=273 19%	15% (10, 21)*

* $p < 0.001$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
** $p < 0.01$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
[a] CDAI < 150
[b] Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)
[c] Decrease of at least 100 points in CDAI from baseline
[d] Discontinuation of corticosteroid and achievement of clinical remission among patients on corticosteroid at baseline
[e] SES-CD ≤ 4 and no individual subscore >1 in any individual variable

Table 25: Proportion of Patients Meeting Primary and Additional Efficacy Endpoints in Induction Study CD-2

CD-2			
Endpoint	**Placebo**	**RINVOQ 45 mg Once Daily**	**Treatment Difference vs Placebo (95% CI)**
Co-Primary Endpoints at Week 12			
Clinical remission[a]			
Total population	N=143 23%	N=295 46%	24% (15, 32)*
Prior biologic failure	N=62 7%	N=135 42%	
Without prior biologic failure	N=81 35%	N=160 50%	

Endoscopic response[b]			
Total population	N=143 13%	N=295 46%	33% (26, 41)*
Prior biologic failure	N=62 10%	N=135 39%	
Without prior biologic failure	N=81 15%	N=160 51%	
Additional Endpoints at Week 12			
Clinical response (CR-100)[c]			
Total population	N=143 40%	N=295 64%	24% (15, 33)*
Prior biologic failure	N=62 25%	N=135 66%	
Without prior biologic failure	N=81 52%	N=160 62%	
Corticosteroid-free clinical remission in patients on CS at baseline[a,d]			
Total population	N=54 13%	N=108 40%	27% (14, 39)*
Prior biologic failure	N=29 7%	N=60 35%	
Without prior biologic failure	N=25 20%	N=48 46%	
Endoscopic remission[e]			
Total population	N=143 8%	N=295 30%	22% (16, 29)*
Prior biologic failure	N=62 3%	N=135 22%	
Without prior biologic failure	N=81 11%	N=160 37%	

* $p < 0.001$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors

[a] CDAI < 150

[b] Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)

[c] Decrease of at least 100 points in CDAI from baseline

[d] Discontinuation of corticosteroid and achievement of clinical remission among patients on corticosteroid at baseline

[e] SES-CD ≤ 4 and no individual subscore >1 in any individual variable

Onset of clinical response based on CDAI was observed as early as two weeks in Studies CD-1 and CD-2, with a greater proportion of patients achieving clinical response at Week 2 in RINVOQ-treated patients compared with placebo.

In Studies CD-1 and CD-2, reductions in stool frequency and abdominal pain were observed in a greater proportion of patients treated with RINVOQ 45 mg induction regimen compared to placebo at Week 12.

In Studies CD-1 and CD-2, patients treated with RINVOQ experienced a clinically meaningful improvement in fatigue, assessed by change from baseline in FACIT-F score, at Week 12, compared to placebo-treated patients. The effect of RINVOQ to improve fatigue after 12 weeks of induction has not been established.

Maintenance Study (CD-3)

The efficacy analysis for CD-3 (NCT03345823) evaluated 343 patients who responded to 12 weeks of RINVOQ 45 mg once daily induction treatment. Patients were re-randomized to receive a maintenance regimen of either RINVOQ 15 mg or 30 mg once daily or placebo for 52 weeks, representing a total of at least 64 weeks of therapy.

The co-primary endpoints of clinical remission (by CDAI) and endoscopic response (by SES-CD) were assessed at Week 52. Secondary efficacy endpoints included corticosteroid-free clinical remission, maintenance of clinical remission, endoscopic remission, and achieving both clinical and endoscopic remission, at Week 52 (see Table 26).

Table 26: Proportion of Patients Meeting Primary and Additional Efficacy Endpoints at Week 52 in Maintenance Study CD-3

Endpoint	Placebo[+]	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily	Treatment Difference 15 mg vs Placebo (95% CI)	Treatment Difference 30 mg vs Placebo (95% CI)
Co-Primary Endpoints					
Clinical remission[a]					
Total population	N=111 14%	N=113 42%	N=119 55%	29% (18, 39)[*]	40% (29, 51)[*]
Prior biologic failure	N=87 13%	N=85 35%	N=90 54%		
Without prior biologic failure	N=24 21%	N=28 61%	N=29 55%		
Endoscopic response[b]					
Total population	N=111 7%	N=113 28%	N=119 41%	22% (13, 32)[*]	34% (25, 44)[*]
Prior biologic failure	N=87 5%	N=85 22%	N=90 42%		
Without prior biologic failure	N=24 17%	N=28 45%	N=29 38%		
Additional Endpoints					
Corticosteroid-free clinical remission[c]					

Total population	N=111 14%	N=113 42%	N=119 53%	29% (18, 39)*	38% (27, 49)*
Prior biologic failure	N=87 13%	N=85 35%	N=90 52%		
Without prior biologic failure	N=24 21%	N=28 61%	N=29 55%		
Maintenance of clinical remission[d]					
Total population	N=73 22%	N=72 51%	N=79 67%	32% (18, 46)*	43% (29, 57)*
Prior biologic failure	N=56 20%	N=50 46%	N=55 69%		
Without prior biologic failure	N=17 29%	N=22 64%	N=24 63%		
Endoscopic remission[e]					
Total population	N=111 5%	N=113 19%	N=119 30%	14% (6, 22)*	25% (15, 34)*
Prior biologic failure	N=87 3%	N=85 14%	N=90 30%		
Without prior biologic failure	N=24 13%	N=28 32%	N=29 31%		
Clinical and endoscopic remission					
Total population	N=111 4%	N=113 16%	N=119 26%	13% (6, 21)*	22% (14, 31)*
Prior biologic failure	N=87 2%	N=85 13%	N=90 26%		
Without prior biologic failure	N=24 8%	N=28 25%	N=29 28%		

[+] The placebo group consisted of patients who achieved clinical response per CDAI with RINVOQ 45 mg at the end of the induction study and were randomized to receive placebo at the start of maintenance therapy.

[*] $p < 0.001$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors

[a] CDAI < 150

[b] Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)

[c] Corticosteroid-free for 90 days prior to Week 52 and achievement of clinical remission. Among the subset of patients who were on corticosteroids at induction baseline, 48% (N=44) in RINVOQ 15 mg group, 44% (N=45) in RINVOQ 30 mg group, and 7% (N=46) in placebo were corticosteroid-free for 90 days prior to Week 52 and in clinical remission.

[d] Defined as achievement of clinical remission at Week 52 in patients who achieved clinical remission at the entry of the maintenance study.

[e] SES-CD ≤ 4 and no subscore > 1 in any individual variable

At Week 52, reductions in stool frequency and abdominal pain were observed in a greater proportion of patients treated with RINVOQ 15 mg and 30 mg compared to placebo.

14.6 Ankylosing Spondylitis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in two randomized, double-blind, multicenter, placebo-controlled trials in patients 18 years of age or older with active ankylosing spondylitis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and Patient's Assessment of Total Back Pain score ≥4.

Trial AS-I (NCT03178487) was a 14-week trial in 187 ankylosing spondylitis patients with an inadequate response to at least two nonsteroidal anti-inflammatory drugs (NSAIDs) or intolerance to or contraindication for NSAIDs and had no previous exposure to biologic DMARDs. At baseline, patients had symptoms of ankylosing spondylitis for an average of 14.4 years and approximately 16% of the patients were on a concomitant cDMARD. Patients received RINVOQ 15 mg once daily or placebo. At Week 14, all patients randomized to placebo were switched to RINVOQ 15 mg once daily. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at Week 14.

Trial AS-II (NCT 04169373) was a 14-week trial in 420 ankylosing spondylitis patients with an inadequate response to 1 or 2 biologic DMARDs. At baseline, patients had symptoms of ankylosing spondylitis for an average of 12.8 years and approximately 31% of the patients were on a concomitant cDMARD. Patients received RINVOQ 15 mg once daily or placebo. At Week 14, all patients randomized to placebo were switched to RINVOQ 15 mg once daily. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at Week 14.

Clinical Response

In both trials, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 27, Figure 5).

Examination of gender, baseline body mass index (BMI), and baseline hsCRP did not identify differences in response to RINVOQ among these subgroups at Week 14.

Table 27: Clinical Response at Week 14

	Trial AS-I bDMARD-naïve			**Trial AS-II bDMARD-IR**		
	PBO (N=94)	**RINVOQ 15 mg (N=93)**	**Difference from PBO (95% CI)**	**PBO (N=209)**	**RINVOQ 15 mg (N=211)**	**Difference from PBO (95% CI)**
ASAS40[a] (%)	25.5	50.5	25 (12, 38)	18.2	44.5	26 (18, 35)
ASAS20[a] (%)	39.4	63.4	24 (10, 38)	38.3	65.4	27 (18, 36)

Abbreviations: ASAS20 (or 40) = Assessment of SpondyloArthritis international Society ≥20% (or ≥40%) improvement; bDMARD = biologic disease modifying anti-rheumatic drug; IR = inadequate responders; PBO = placebo
[a] An ASAS20 (ASAS40) response is defined as a ≥20% (≥40%) improvement and an absolute improvement from baseline of ≥1 (≥2) unit(s) (range 0 to 10) in ≥3 of 4 domains (Patient Global, Total Back Pain, Function, and Inflammation), and no worsening in the potential remaining domain (defined as worsening ≥20% and ≥1 unit for ASAS20 or defined as worsening of > 0 units for ASAS40).
For binary endpoints, Week 14 results are based on non-responder imputation (Trial AS-I) and on non-responder imputation in conjunction with multiple imputation (Trial AS-II).

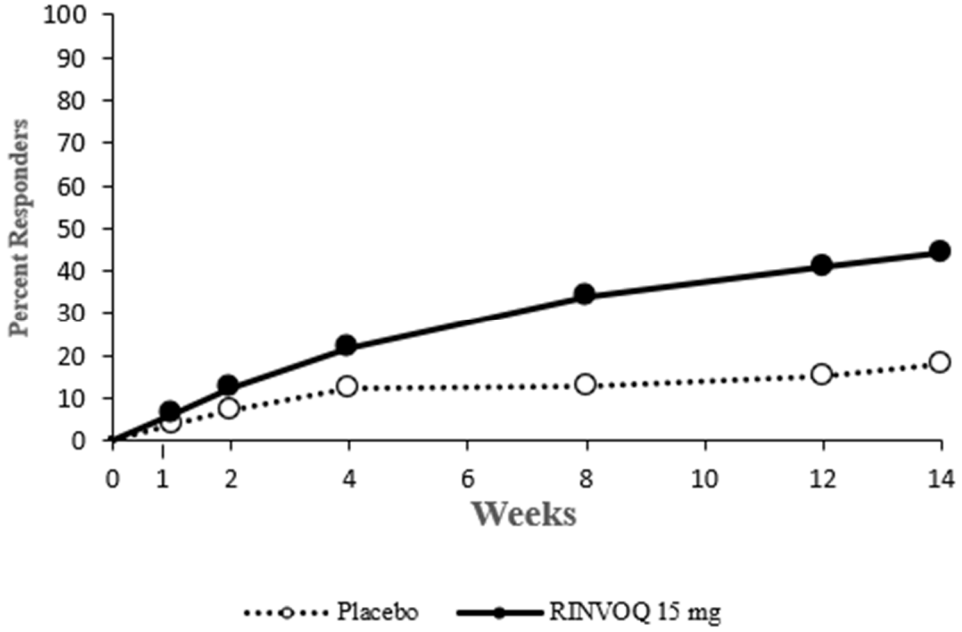
Treatment with RINVOQ 15 mg resulted in improvements in the individual components of the ASAS40 response criteria compared to placebo (Table 28).

Table 28: ASAS Components and Other Measures of Disease Activity[a]

	Trial AS-I bDMARD-naïve		**Trial AS-II bDMARD-IR**	
Treatment Group	**PBO**	**RINVOQ 15 mg**	**PBO**	**RINVOQ 15 mg**
N	94	93	209	211
Patient Global Assessment of Disease Activity[b]				
Baseline	6.8 (1.66)	6.6 (1.81)	7.2 (1.40)	7.4 (1.48)
Week 14	5.4 (1.97)	3.8 (2.44)	5.9 (2.13)	4.3 (2.36)
Total Back Pain[b]				
Baseline	6.7 (1.78)	6.8 (1.77)	7.4 (1.43)	7.5 (1.48)
Week 14	5.0 (2.27)	3.7 (2.39)	5.9 (2.09)	4.4 (2.48)
BASFI[b]				
Baseline	5.54 (2.17)	5.35 (2.36)	6.18 (1.87)	6.28 (2.03)
Week 14	4.21 (2.26)	3.14 (2.37)	5.09 (2.21)	3.98 (2.45)
Inflammation[c]				
Baseline	6.66 (1.90)	6.51 (1.99)	6.75 (1.55)	6.88 (1.84)
Week 14	4.61 (2.13)	3.40 (2.16)	5.11 (2.30)	3.87 (2.50)
hsCRP (mg/L)				
Baseline	11.02 (10.85)	8.90 (12.42)	14.71 (17.54)	15.30 (20.53)
Week 14	11.72 (15.93)	2.23 (3.56)	15.31 (17.55)	3.82 (8.26)

Abbreviations: ASAS = Assessment of SpondyloArthritis international Society; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease modifying anti-rheumatic drug; hsCRP = high sensitivity C-reactive protein; IR = inadequate responder; PBO = placebo; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index
Results are based on as-observed data from patients who have baseline observation.
[a] Data shown are mean (standard deviation).
[b] Numeric rating scale (NRS): 0 = best, 10 = worst
[c] mean of BASDAI questions 5 and 6 assessing morning stiffness severity and duration: 0 = best, 10 = worst

Figure 5. Percent of Patients Achieving ASAS40 in Trial AS-II*



*Results are based on non-responder imputation in conjunction with multiple imputation.

Other Health-Related Outcomes

In Trial AS-II, patients treated with RINVOQ 15 mg showed significant improvements in health-related quality of life as measured by Ankylosing Spondylitis Quality of Life (ASQoL) compared to placebo at Week 14. In Trial AS-I, improvement in ASQoL compared to placebo was also observed.

Enthesitis

In Trial AS-II, patients with pre-existing enthesitis treated with RINVOQ 15 mg showed significant improvement in enthesitis compared to placebo as measured by change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Week 14. In Trial AS-I, improvement in MASES compared to placebo was also observed.

Spinal mobility

In Trial AS-II, patients treated with RINVOQ 15 mg showed significant improvement in spinal mobility compared to placebo as measured by change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14. In Trial AS-I, improvement in BASMI compared to placebo was also observed.

14.7 Non-radiographic Axial Spondyloarthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in a randomized, double-blind, multicenter, placebo-controlled trial in patients 18 years of age or older with active non-radiographic axial spondyloarthritis. Trial nr-axSpA (NCT04169373) was a 52-week placebo-controlled trial in 314 patients (of which 313 patients received study treatment) with active non-radiographic axial spondyloarthritis with an inadequate response to at least two nonsteroidal anti-inflammatory drugs (NSAIDs) or intolerance to or contraindication for NSAIDs. Patients must have had objective signs of inflammation indicated by elevated C-reactive protein (CRP) (defined as > upper limit of normal), and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 numerical rating scale (NRS) at the Screening and Baseline Visits. At baseline, approximately 29.1% of the patients were on a concomitant cDMARD. 32.9% of the patients had an inadequate response or intolerance to bDMARD therapy. Patients received RINVOQ 15 mg once daily or placebo. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at Week 14.

Clinical Response

In Trial nr-axSpA, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 29, Figure 6).

Examination of gender, baseline BMI, symptom duration of non-radiographic axial spondyloarthritis, baseline hsCRP, MRI sacroiliitis, and prior use of bDMARDs did not identify differences in response to RINVOQ among these subgroups at Week 14.

Table 29: Clinical Response at Week 14

	PBO (N=157)	**RINVOQ 15 mg (N=156)**	**Difference from PBO (95% CI)**
ASAS40[a] (%)	22.3	44.9	22.5 (12.4, 32.5)
ASAS20[a] (%)	43.3	66.7	23.2 (12.6, 33.8)

Abbreviations: ASAS20 (or 40) = Assessment of SpondyloArthritis international Society ≥20% (or ≥40%) improvement; PBO = placebo

[a] An ASAS20 (ASAS40) response is defined as a ≥20% (≥40%) improvement and an absolute improvement from baseline of ≥1 (≥2) unit(s) (range 0 to 10) in ≥3 of 4 domains (Patient Global, Total Back Pain, Function, and Inflammation), and no

worsening in the potential remaining domain (defined as worsening ≥20% and ≥1 unit for ASAS20 or defined as worsening of > 0 units for ASAS40).
For binary endpoints, results are based on non-responder imputation in conjunction with multiple imputation.

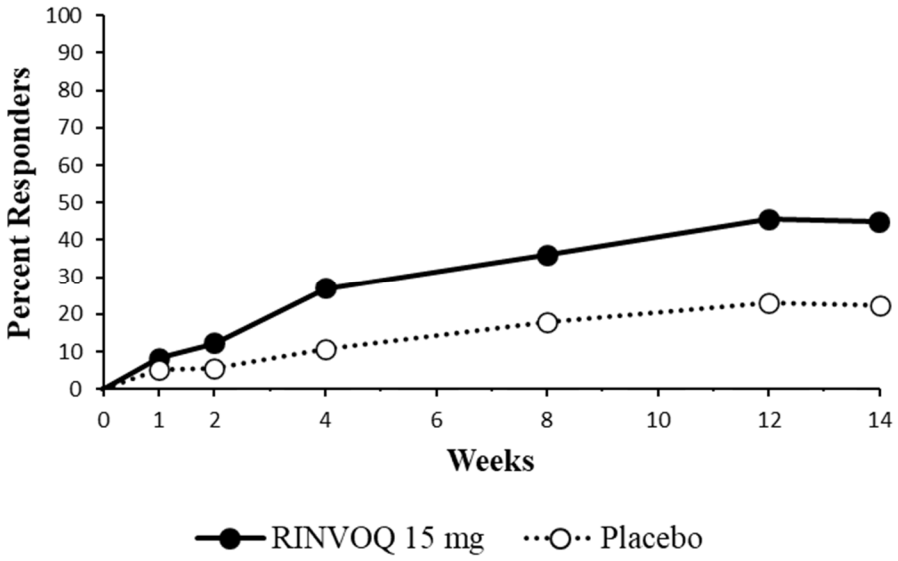
Treatment with RINVOQ 15 mg resulted in improvements in the individual components of the ASAS40 response criteria compared to placebo (Table 30).

Table 30: ASAS Components and Other Measures of Disease Activity[a]

Treatment Group	**PBO (N=157)**	**RINVOQ 15 mg (N=156)**
Patient Global Assessment of Disease Activity[b]		
Baseline	7.30 (1.38)	6.99 (1.62)
Week 14	5.35 (2.31)	4.16 (2.38)
Total Back Pain[b]		
Baseline	7.29 (1.39)	7.23 (1.55)
Week 14	5.27 (2.36)	4.29 (2.49)
BASFI[b]		
Baseline	5.99 (2.14)	5.89 (2.08)
Week 14	4.47 (2.42)	3.33 (2.39)
Inflammation[c]		
Baseline	6.68 (1.67)	6.60 (1.83)
Week 14	4.69 (2.36)	3.48 (2.51)
hsCRP (mg/L)		
Baseline	8.75 (12.91)	9.93 (16.17)
Week 14	7.25 (10.61)	2.84 (4.90)

Abbreviations: ASAS = Assessment of SpondyloArthritis international Society; BASFI = Bath Ankylosing Spondylitis Functional Index; hsCRP = high sensitivity C-Reactive Protein; PBO = placebo
[a] Data shown are mean (standard deviation).
[b] Numeric rating scale (NRS): 0 = best, 10 = worst
[c] mean of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions 5 and 6 assessing morning stiffness severity and duration: 0 = best, 10 = worst

Figure 6. Percent of Patients Achieving ASAS40*



*Results are based on non-responder imputation in conjunction with multiple imputation.

Other Health-Related Outcomes

Patients treated with RINVOQ 15 mg showed significant improvements in health-related quality of life as measured by Ankylosing Spondylitis Quality of Life (ASQoL) compared to placebo at Week 14.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RINVOQ extended-release tablets are supplied as:

- 15 mg: purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side.

  30 tablets in a bottle; NDC: 0074-2306-30

- 30 mg: red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side.

  30 tablets in a bottle; NDC: 0074-2310-30

- 45 mg: yellow to mottled yellow, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a45’ on one side.

  28 tablets in a bottle; NDC: 0074-1043-28

Storage and Handling

Store at 2˚C to 25˚C (36˚F to 77˚F).

Store in the original bottle in order to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ.

Advise patients that exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events

Inform patients that RINVOQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions (5.4)]*.

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions (5.6)]*.

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDs, corticosteroids, or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions (5.7)]*.

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ *[see Adverse Reactions (6.1)]*.

Laboratory Abnormalities

Inform patients that RINVOQ may affect certain lab tests, and that blood tests are required before and during RINVOQ treatment *[see Warnings and Precautions (5.8)]*.

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ prior to a potential vaccination *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations (8.3)]*.

Advise females patients who are exposed to RINVOQ during pregnancy to contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Lactation

Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the last dose *[see Use in Specific Populations (8.2)]*.

Administration

Advise patients not to chew, crush, or split RINVOQ tablets *[see Dosage and Administration (2.2)]*.

Advise patients to avoid food or drink containing grapefruit during treatment with RINVOQ *[see Drug Interactions (7.1)]*.

Medication Residue in Stool

Instruct patients to notify their healthcare provider if they repeatedly notice medication residue (e.g., intact RINVOQ tablet or fragments) in stool or ostomy output *[see Warnings and Precautions (5.11)]*.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, USA

20078707 May 2023

MEDICATION GUIDE
RINVOQ® (RIN-VOKE)
(upadacitinib)
extended-release tablets, for oral use

What is the most important information I should know about RINVOQ?
RINVOQ can cause serious side effects, including:

1. Serious Infections.

RINVOQ is a medicine that affects your immune system. RINVOQ can lower the ability of your immune system to fight infections. Some people have had serious infections while taking RINVOQ, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting treatment with RINVOQ.
- Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with RINVOQ.
- You should not start taking RINVOQ if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster).
- **Before starting RINVOQ, tell your healthcare provider if you**:
  - are being treated for an infection.
  - have had an infection that does not go away or that keeps coming back.
  - have diabetes, chronic lung disease, HIV, or a weak immune system.
  - have TB or have been in close contact with someone with TB.
  - have had shingles (herpes zoster).
  - have or have had hepatitis B or C.
  - live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use RINVOQ. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
  - think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills
    - shortness of breath
    - warm, red, or painful skin or sores on your body
    - muscle aches
    - feeling tired
    - blood in your phlegm
    - diarrhea or stomach pain
    - cough
    - weight loss
    - burning when you urinate or urinating more often than usual

After starting RINVOQ, call your healthcare provider right away if you have any symptoms of an infection. RINVOQ can make you more likely to get infections or make worse any infections that you have. If you get a serious infection, your healthcare provider may stop your treatment with RINVOQ until your infection is controlled.

2. Increased risk of death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and are taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors. RINVOQ is a JAK inhibitor medicine.

3. Cancer and immune system problems.

RINVOQ may increase your risk of certain cancers by changing the way your immune system works.

Lymphoma and other cancers, including skin cancers can happen in people taking RINVOQ. People taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors have a higher risk of certain cancers including lymphoma and lung cancer, especially if you are a current or past smoker.

Tell your healthcare provider if you have ever had any type of cancer. Follow your healthcare provider's advice about having your skin checked for skin cancer during treatment with RINVOQ. Limit the amount of time you spend in sunlight. Avoid using tanning beds or sunlamps. Wear protective clothing when you are in the sun and use a sunscreen with a high protection factor (SPF 30 and above). This is especially important if your skin is very fair or if you have a family history of skin cancer.

4. Increased risk of major cardiovascular events such as heart attack, stroke or death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and taking a medicine in the class of medicines called JAK inhibitors, especially if you are a current or past smoker.

Get emergency help right away if you have any symptoms of a heart attack or stroke while taking RINVOQ, including:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded
- weakness in one part or on one side of your body
- slurred speech

5. Blood Clots (thrombosis).
Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) and arteries (arterial thrombosis) can happen in some people taking RINVOQ. This may be life-threatening and cause death. Blood clots in the veins of the legs (DVT) and lungs (PE) have happened more often in people who are 50 years of age and older and with at least 1 heart disease (cardiovascular) risk factor taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors.

- Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
- Get medical help right away if you have signs and symptoms of blood clots during treatment with RINVOQ, including:
  - swelling
  - pain or tenderness in one or both legs
  - sudden unexplained chest or upper back pain
  - shortness of breath or difficulty breathing

6. Allergic reactions. Symptoms such as rash (hives), trouble breathing, feeling faint or dizzy, or swelling of your lips, tongue, or throat, that may mean you are having an allergic reaction have been seen in people taking RINVOQ. Some of these reactions were serious. If any of these symptoms occur during treatment with RINVOQ, stop taking RINVOQ and get emergency medical help right away.

7. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking RINVOQ can get tears in their stomach or intestines. This happens most often in people who take nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.
- Get medical help right away if you get stomach-area pain, fever, chills, nausea, or vomiting.

8. Changes in certain laboratory test results.
Your healthcare provider should do blood tests before you start taking RINVOQ and while you take RINVOQ to check for the following:

- **low neutrophil and lymphocyte counts.** Neutrophils and lymphocytes are types of white blood cells that help the body fight off infections.
- **low red blood cell counts.** Red blood cells carry oxygen. Low red blood cells means you may have anemia, which may make you feel weak and tired.
- **increased cholesterol levels.** Your healthcare provider should do blood tests to check your cholesterol levels approximately 12 weeks after you start taking RINVOQ, and as needed.
- **elevated liver enzymes.** Liver enzymes help to tell if your liver is functioning normally. Elevated liver enzymes may indicate that your healthcare provider needs to do additional tests on your liver.

You should not take RINVOQ if your neutrophil count, lymphocyte count, or red blood cell count is too low or your liver tests are too high. Your healthcare provider may stop your RINVOQ treatment for a period of time if needed because of changes in these blood test results.

See **"What are the possible side effects of RINVOQ?"** for more information about side effects.

What is RINVOQ?
RINVOQ is a prescription medicine that is a Janus kinase (JAK) inhibitor. RINVOQ is used:

- to treat adults with moderate to severe rheumatoid arthritis when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults with active psoriatic arthritis when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults and children 12 years of age and older with moderate to severe eczema (atopic dermatitis) that did not respond to previous treatment and their eczema is not well controlled with other pills or injections, including biologic medicines, or the use of other pills or injections is not recommended.
- to treat adults with moderate to severe ulcerative colitis when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults with moderate to severe Crohn's disease when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults with active ankylosing spondylitis when 1 or more medicines called tumor necrosis factor (TNF) blockers have been used, and did not work well or could not be tolerated.
- to treat adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation when a tumor necrosis factor (TNF) blocker medicine has been used, and did not work well or could not be tolerated.

RINVOQ is safe and effective in children 12 years of age and older weighing at least 88 pounds (40 kg) with atopic dermatitis.

It is not known if RINVOQ is safe and effective in children with juvenile idiopathic arthritis, with psoriatic arthritis, with ankylosing spondylitis, or with non-radiographic axial spondyloarthritis.

It is not known if RINVOQ is safe and effective in children under 12 years of age with atopic dermatitis.

It is not known if RINVOQ is safe and effective in children with ulcerative colitis or with Crohn's disease.

Do not take RINVOQ if you are allergic to upadacitinib or any of the ingredients in RINVOQ. See the end of this Medication Guide for a complete list of ingredients in RINVOQ.

Before taking RINVOQ, tell your healthcare provider about all of your medical conditions, including if you:

- See **"What is the most important information I should know about RINVOQ?"**
- have an infection.
- are a current or past smoker.
- have had a heart attack, other heart problems, or stroke.
- have liver problems.
- have kidney problems.
- have unexplained stomach (abdominal) pain, have a history of diverticulitis or ulcers in your stomach or intestines, or are taking NSAIDs.
- have low red or white blood cell counts.
- have recently received or are scheduled to receive an immunization (vaccine). People who take RINVOQ should not receive live vaccines.
- are pregnant or plan to become pregnant. Based on animal studies, RINVOQ may harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will check whether or not you are pregnant before you start treatment with RINVOQ.
  - You should use effective birth control (contraception) to avoid becoming pregnant during treatment with RINVOQ and for 4 weeks after your last dose of RINVOQ.
  - Tell your healthcare provider if you think you are pregnant or become pregnant during treatment with RINVOQ.
  - If you take RINVOQ during pregnancy, contact AbbVie Inc. at 1-800-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch to provide information about the health of you and your baby.
- are breastfeeding or plan to breastfeed. RINVOQ may pass into your breast milk. You and your healthcare provider should decide if you will take RINVOQ or breastfeed. **Do not** breastfeed during treatment with RINVOQ and for 6 days after your last dose of RINVOQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. RINVOQ and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- medicines for fungal infections (such as ketoconazole, itraconazole, posaconazole or voriconazole) or clarithromycin (for bacterial infections) as these medicines may increase the amount of RINVOQ in your blood.
- rifampicin (for bacterial infections) or phenytoin (for neurological disorders) as these medicines may decrease the effect of RINVOQ.
- medicines that affect your immune system (such as azathioprine and cyclosporine) as these medicines may increase your risk of infection.

Ask your healthcare provider or pharmacist, if you are not sure if you are taking any of these medicines.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take RINVOQ?

- Take RINVOQ exactly as your healthcare provider tells you to use it.
- Take RINVOQ 1 time a day with or without food.
- Swallow RINVOQ tablets whole. Do not split, crush, or chew the tablets.
- If you take too much RINVOQ, call your healthcare provider or poison control center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What should I avoid while taking RINVOQ?

Avoid food or drink containing grapefruit during treatment with RINVOQ. Eating grapefruit or drinking grapefruit juice may increase the risk of side effects.

What are the possible side effects of RINVOQ?

RINVOQ may cause serious side effects, including:

- See **"What is the most important information I should know about RINVOQ?"**

The most common side effects of RINVOQ in people treated for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis include:

- upper respiratory tract infections (common cold, sinus infections)
- shingles (herpes zoster)
- herpes simplex virus infections, including cold sores
- bronchitis
- nausea
- cough
- fever
- acne
- headache

The most common side effects of RINVOQ in people treated for atopic dermatitis include:

- upper respiratory tract infections (common cold, sinus infections)
- acne
- herpes simplex virus infections, including cold sores
- headache
- increased blood levels of creatine phosphokinase
- cough
- allergic reactions
- inflammation of hair follicles
- nausea
- stomach-area (abdominal) pain
- fever
- increased weight
- shingles (herpes zoster)
- flu
- tiredness
- low white blood cell count (neutropenia)
- muscle pain
- flu-like illness

The most common side effects of RINVOQ in people treated for ulcerative colitis include:

- upper respiratory tract infections (common cold, sinus infections)
- acne
- herpes simplex virus infections, including cold sores
- inflammation of the hair follicles
- rash
- flu
- shingles (herpes zoster)
- increased blood cholesterol levels
- increased blood levels of creatine phosphokinase
- increased liver enzyme levels
- low number of certain types of white blood cells (neutropenia, lymphopenia)

The most common side effects of RINVOQ in people treated for Crohn's disease include:

- upper respiratory tract infections (common cold, sinus infections)
- bronchitis
- pneumonia
- flu
- acne
- herpes simplex virus infections, including cold sores
- tiredness
- cough
- fever
- shingles (herpes zoster)
- headache
- increased blood levels of creatine phosphokinase
- increased liver enzyme levels
- low number of red blood cells (anemia)
- low number of white blood cells (neutropenia, leukopenia)
- infection of the stomach and intestine (gastroenteritis)

Separation or tear to the lining of the back part of the eye (retinal detachment) has happened in people with atopic dermatitis treated with RINVOQ. Call your healthcare provider right away if you have any sudden changes in your vision during treatment with RINVOQ.

Some people taking RINVOQ may see medicine residue (a whole tablet or tablet pieces) in their stool. If this happens, call your healthcare provider.

These are not all the possible side effects of RINVOQ.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RINVOQ?

- Store RINVOQ between 36°F to 77°F (2°C to 25°C).
- Store RINVOQ in the original bottle to protect it from moisture.
- **Keep RINVOQ and all medicines out of the reach of children.**

General information about the safe and effective use of RINVOQ.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RINVOQ for a condition for which it was not prescribed.
Do not give RINVOQ to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about RINVOQ that is written for health professionals.

What are the ingredients in RINVOQ 15 mg tablets?
Active ingredient: upadacitinib

Inactive ingredients: colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

What are the ingredients in RINVOQ 30 mg tablets?

Active ingredient: upadacitinib

Inactive ingredients: colloidal silicon dioxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

What are the ingredients in RINVOQ 45 mg tablets?

Active ingredient: upadacitinib

Inactive ingredients: colloidal silicon dioxide, hypromellose, iron oxide yellow and iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, USA

RINVOQ® is a registered trademark of AbbVie Biotechnology Ltd.

For more information, call 1-800 2-RINVOQ (1-800-274-6867) or go to www.RINVOQ.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 5/2023

20078707